25 January 2018

Ms. Dana Friedman
Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-8015

Submitted via Regulations.gov EPA-HQ-OPP-2012-0330

RE: Registration Reviews; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides, December 15, 2017; Fed. Reg 82: 59596; FR Doc No: 2017-27098; Docket ID: EPA-HQ-OPP-2012-0330.

Dear Ms. Friedman:

CropLife America (CLA) appreciates the opportunity to provide comment to the U.S. Environmental Protection Agency (EPA or Agency), Office of Pesticide Programs (OPP) on its Registration Reviews; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides, EPA-HQ-OPP-2012-0330; and on its use of the "Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides," (Framework) EPA-HQ-OPP-0316-DRAFT-0075.pdf.[1]

Established in 1933, CLA represents the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all the vital and necessary crop protection and biotechnology products used by American farmers, ranchers and landowners. CLA is committed to working with EPA, as the primary federal agency responsible for the regulation of pesticides, to encourage practical, science-based regulation of its members' products.

CLA provided suggestions on the "Draft Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides" (Draft Framework), as part of its April 8, 2016 comments on the EPA Docket for the FIFRA Scientific Advisory Panel on chlorpyrifos.[2] By reference, those comments are incorporated herein. To summarize the CLA comments on the Draft Framework, we extract the following from the CLA comments of April 8, 2016.

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[1] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident. Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

[2] US EPA. FIFRA Scientific Advisory Panel (FIFRA SAP) to consider and review Chlorpyrifos: Analysis of Biomonitoring Data, March 8, 2016; FR Doc No: 2016-05174; Docket ID: EPA-HQOPP-2016-0062-0001.

In its Draft Framework EPA refers to use of a modified Bradford Hill[3] criteria approach to assessing strength and appropriate use of epidemiological studies in human health risk assessment. The criteria support sound approaches to evaluating associations in epidemiological data cohorts but are not intended to be used to establish a cause and effect association between exposure and health or environmental impact. It is important to note that even when primary data are available for statistical reassessment, epidemiological studies are not intended to replace toxicological data collected from animal studies intended to establish effects in studies.

EPA did not incorporate CLA's comments into the Framework. Nevertheless, CLA and its member companies continue to believe that a consistent and scientifically defensible approach to use of all sources of data in regulatory decision making is required. For this reason, CLA does not support the weight of evidence approach taken by EPA in integration of literature, epidemiologic, and other sources of study outcomes in its regulatory decision making.

The Framework contains sound scientific principles, but it is incomplete and does not consider the practitioner perspective. CLA submits a detailed report, "Comments on Office of Pesticide Programs' Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides (Framework)," attached hereto intended to highlight the Framework's limitations and EPA's missteps in its development of it. We welcome the opportunity to work with EPA to correct some of the missteps that have occurred, and importantly that have negatively impacted our members' registration timelines and outcomes.

CLA's comments are intended to address the lack of consistency in approach taken by EPA, relative to the recommendations in the Framework. Risk assessment approaches including various sources of information and data, and inconsistent use of study outcomes within a study when reported across various health outcomes, limit consistency and predictability to assessments intended to follow the Framework.

We continue to welcome the opportunity to work with EPA and other Federal Agencies in pursuit of scientifically balanced approaches to human health risk assessment. Should you have questions or wish to discuss these issues further, please contact me directly [(jcollins@croplifeamerica.org) or (+1) 202-833-4474].

Thank you for your consideration of these comments.

Respectfully,

Janet E. Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs

Cc: Mr. Rick Keigwin

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[3] Hill A. B., 1965. "The environment and disease: Association or causation?" Proc R Soc Med 58, pp 295-380.

Comments on Office of Pesticide Programs' 2016 "Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides" (Framework).

Framework Issue Date: December 28, 2016.

Accessed: https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

Key findings.

The 2016 Framework incorporates some aspects of the 2010 SAP recommendations for change to the Draft Framework. Notably, the 2016 Framework document devotes more attention to study quality. However, there remain important limitations. The Framework is "final" and will be updated on as-needed basis.

Missed opportunity. The Office of Pesticide Programs[4] (OPP) provides no guidance to epidemiologists or funding agencies about what is required for risk assessment. As a result, there is little value to sharing this document with other epidemiologists. They will merely say, yes, we know the difference between case control and cohort studies. Similarly, OPP does not offer any recommendations to change the status quo with respect to study limitations, data access or interpretation of epidemiology data.

This is not a framework for integration with toxicology[2]. There is little discussion or even recognition about the state of the science of registered pesticides. The OPP Framework reads as if all epidemiology studies are new discoveries on new pesticides. The Framework makes little effort to incorporate the known with the new. OPP cannot both require GLP studies for pesticide active ingredients and then turn a blind eye to those results when evaluating epidemiology studies.

"Weight of Evidence" is poorly defined. Elements of the Bradford Hill Criteria are listed but the descriptions permit any interpretation.

What about the "missing" or unpublished data? There are multiple places in the Framework that beg for a conversation about access to data. In Section IIIA, OPP mentions missing data. Section IV discusses statistical analyses and null results. If indeed there are missing data or incomplete analyses, OPP should be recommending a discussion with OPP, the registrant(s), and the epidemiology investigators to develop a plan to make the missing data available and/or conduct additional analyses. This is not present in the 2016 Framework.

[4] Interchange OPP and Framework in "saying" and "recommending". We use the term OPP for the US EPA OPP. [2] In toxicology, the terms toxicology, *in vivo* and Guideline Studies are used interchangeably. There are differences, but are considered similarly for the purposes of comparing them to human epidemiology data.

Study quality evaluation will not be transparent. Tables of ideal study elements and quality criteria are part of the Framework. However, there is little direction or discussion regarding how these will be used or how individual studies will be scored. The OPP has previously classified epidemiology studies as being of high and medium quality without providing the details of its interpretation on individual elements.

Incident data should be "complementary." OPP recommends that incident data can provide useful, complementary information for real world risk of pesticides. Complementary is the critical point, all data should be evaluated together.

Contents

Opportunities for dialogue and discussion with OPP.

What are their messages to epidemiologists and funders?

How will they OPP integrate epidemiology results with toxicology results?

What is the difference between regulatory science and discovery science? For toxicology? For epidemiology?

What is the solution for publication bias, and lack of published information on null results?

If a publication does not provide full disclosure of analyses, sensitivity, confounding, or dose-response, does OPP have a plan or requirement to either have the authors complete the required analyses or to acquire the raw data?

What is the vision for registrant requirements in the future? Will epidemiology be required?

Recommendations from the 2010 SAP[5]:

The February 2 – 4, 2010 FIFRA Scientific Advisory Panel (SAP) evaluated the Draft Framework on epidemiology and provided extensive comments. Several topics are highlighted.

Integration of multidisciplinary data.

The SAP noted that the 2010 Draft Framework described problem formulation but did not indicate specifically how the toxicological and epidemiologic information would be "considered in an integrated fashion." For example, the SAP suggested that an integrated approach would identify limitations with a recommendation for additional research. Other recommendations:

1. Define "biological plausibility." Several interpretations of plausibility are possible. Emphasis should be placed on dose-response relationships, temporal sequence, strength of the association and consistency of findings across studies.

[5] Minutes published on April 22, 2010 regarding the "Draft framework and case studies on atrazine, human incidents, and the Agricultural Health Study: Incorporation of epidemiology and human incident data into human health risk assessment."

2. Use the "source to adverse outcome pathway" to identify critical data gaps.
3. The SAP discussed making a logical progression from the key events in animal studies. It is important to consider the relevancy across species from high dosing that is unlikely to occur in humans and to separately consider differences in physiology or biology.

□ What strong epidemiology studies look like.

Robust epidemiology studies are characterized by strong design with well-characterized exposures. However, all studies have weaknesses. "The Agency needs to remain cognizant of those when considering use of data from any single study or an aggregation of studies for a specific pesticide." The 2010 SAP recommended the Agency establish a set of quality criteria. Quality elements include:

1. Validation of exposure assessment
2. Adequate sample size
3. Well defined outcome (disease vs. not diseased)
4. Attention to reduced sources of bias
5. Control for confounding and identification of effect modifying factors
6. Potential for generalizing to other populations.

□ Exposure

1. Exposure must be robustly and quantitatively addressed. Exposure should be paired with identification of key events in a mode of action context.
2. "[E]xposure assessment should be evaluated for accuracy, precision and reliability, and should include validation where feasible… Exposure metrics can represent dose estimates (for example average daily dose or peak dose), duration of exposure, or a combination of these in a cumulative exposure metric."

Elements of the 2016 Framework.

OPP characterizes the 2016 Framework as a description of overall conceptual scientific consideration when evaluating epidemiology studies. It is not intended to be binding or serve as a reviewer's guide. OPP states on page three, that "since the number of pesticides for which quality epidemiology data either exist or are being developed remains relatively low in the near term, experimental laboratory data will likely continue to be the primary source of data for use in quantitative risk assessment for most pesticides."

Interpretation: The page three statement implies that for pesticides with some epidemiology data, experimental data may be supplanted with epidemiology data. It also suggests that epidemiology results will be used more frequently in the future.

This Framework is a "final" document. OPP says that will be updated from time-to-time and on an as needed basis.

II. Introduction

OPP lists uses of human data.

1. Provide insight in effects caused by actual chemical exposures
2. Guide additional analyses (doses, endpoint selection)
3. Identify potentially susceptible population
4. Identify new health effects
5. Confirm the existing toxicological observations

OPP discusses the NRC 2007 Tox21 report, in that a strong WOE draws from the "best available information" from multiple data sources. The Framework presents existing guidance documents and continues to draw from the Bradford Hill criteria (guideline elements). OPP recognizes that epidemiology studies tend to report on widely used pesticides, which also have a significant body of data from toxicology, exposure, pharmacokinetics, MOA and AOP, etc. On page five, OPP states that "it is noteworthy that the availability of a fully elucidated MOA/AOP is not [a] requirement for using epidemiology studies in human health risk assessment."

Interpretation: The Framework recommends using multiple data sources. We might interpret this as OPP will use toxicology when reviewing epidemiology. It is also possible (and likely) that OPP is using this as mandate that it must use epidemiology, to the exclusion of toxicology.

III Systematic review in pesticide risk assessment: Epidemiology

A. Problem Formulation

Here OPP describes how it plans to define the scope of an analysis. OPP continues to point out that a review may be focused on exposure pathways and certain health outcomes. It notes (page nine), "If missing data are critical to the assessment, options are discussed as to how best to obtain that information."

Interpretation: This section lists many questions that would be considered. At first look, it seems like a good practice. However, it is unclear if these are standard questions posed for all pesticides and risk assessments or if they are raised after reviewing an epidemiology publication. The comment about missing data is an opportunity for enhancement to the Framework. Indeed, the Framework does not list how to obtain missing data. If indeed there are missing data, there should be a discussion among OPP, registrant(s), and the epidemiology investigators to develop a plan to make the missing data available.

B. Data Collection

This section details how OPP will search and report on published and unpublished sources. On page 10 of the Framework, it states, "In the case of epidemiology, most studies are expected to be found in the open scientific literature. Although in some cases supplemental analyses or information may be available, dialogue with the researchers may provide additional, important information not published in the original paper in understanding and interpreting epidemiology studies."

Interpretation. It is a good practice to assure the reader that OPP will not selectively pick certain studies. However, if indeed OPP is willing to use epidemiology data *in lieu* of toxicology, waiting

for epidemiology studies to be conducted, and reported seems unduly random. If epidemiology data are important, the process to conduct and report should be more systematic.

C. Data Evaluation

OPP promises to use study quality in its review. More on this later in IV.C.

D. Data integration: Weight of Evidence (WOE)

OPP promises to use a WOE analysis, and that conclusions will be made on the preponderance of information rather than relying on any one study. Specific aspects are listed:

- Key events. The events can come from the MOA/AOP, PK or any human or animal study. In other words, there is no guideline.
- Dose-response. A well-characterized exposure-response relationship strongly suggests cause and effect in epidemiology studies.
- Temporal association. This is another argument in favor of casualty.
- Consistency. A pattern across several independent studies supports causality. OPP also states that discordant results cannot be used to rule out a causal connection.
- Strength of association. A large and precise risk increases confidence in a true association. OPP also states that a small effect can also be important.
- Specificity of the association. Specificity may or may not be a strong argument for causation.
- Coherence. When animal and human data show a similar toxic profile, there is high confidence in the human health risk assessment. If they are dissimilar it is important to consider other factors.
- Biological plausibility. A proposed mechanism is an important source of support for causality. Lack of mechanistic data is not a reason to reject causality.

Interpretation: These elements are the Bradford Hill Criteria. For many elements, OPP first makes a strong point and then gives an excuse to dismiss it. In other words, the list is correct but the interpretation is weak. These elements were designed the be used collectively to dispassionately evaluate a body of literature. When there is evidence of a causal effect, the reviewer does not have to offer excuses for each element.

The Hill criteria have been criticized because reviewers can pick and choose certain elements. Further they do not consider bias and confounding. However, reproducibility in independently conducted studies should correct for errors in any individual study. In its Framework, OPP is providing no guidance at all for WOE.

E. Overall conclusion, recommendation for risk assessment, statement of areas of confidence and uncertainty.

Epidemiology studies have the potential to inform multiple components of the risk assessment.

IV. Reviewing epidemiology studies for use in pesticide risk assessment

A. Introduction

This section gives the merits of epidemiology. It recognizes that exposures (to pesticides) have changed (declined) over time. This is important when reviewing a body of literature.

Epidemiology data study real-world chemical exposures in humans and provide information on hazard/risk characterization. The results can be used to guide future research. It also can inform uncertainties associated with specific extrapolation.

Interpretation. No argument. Of course, devil lies in the details.

B. Types of epidemiology studies

This section reads like an epidemiology textbook. OPP describes the type of study and when each is used.

C. Evaluating epidemiology studies for use in pesticide risk assessment

The Framework also has a table on page 24 with five parameters for quality consideration ranked as high/moderate/low. On page 22, OPP uses a list of eight aspects that are considered important (listed below). These include:

1. Clear articulation of the hypothesis, even if the study is hypothesis-generating in nature;
2. Adequate assessment of exposure for the relevant critical windows of the health effects, the range of exposure of interest for the risk assessment target population, and the availability of a dose/exposure-response trend from the study, among other qualities of exposure assessment;
3. Reasonably valid and reliable outcome ascertainment (the correct identification of those with and without the health effect in the study population);
4. Appropriate inclusion and exclusion criteria that result in a sample population representative of the target population, and absent systematic bias;
5. Adequate measurement and analysis of potentially confounding variables, including measurement or discussion of the role of multiple pesticide exposure, or mixtures exposure in the risk estimates observed;
6. Overall characterization of potential systematic biases in the study including errors in the selection of participation and in the collection of information; this can include performing sensitivity analysis to determine the potential influence of systematic error on the risk estimates presented;
7. Evaluation of the statistical power of the study to observe health effects with appropriate discussion and/or presentation of power estimates; and,
8. Use of appropriate statistical modeling techniques, given the study design and the nature of the outcomes under study. "

Interpretation: As we saw with the glyphosate and organophosphate (OP) reviews, these aspects/considerations are reasonable but OPP *application* of them is important. The terms of "good," "adequate," and "appropriate" are highly subjective. Further, there is no discussion in the Framework about interpretation of study quality if one or more parameter scores has a low score. Previously, OPP had not revealed how it scored each parameter but only gave how the overall study was ranked. Transparency in these elements is an important "ask" for future assessments.

9. Exposure assessment

The Framework goes into detail about direct and indirect approaches. It incorporates the biomarker evaluation instrument (BEES-C) from Lakind et al. (2014).[6]

Interpretation. The validity of an exposure assessment is more important than defining if it is direct or indirect. OPP omitted the consideration of Exposure Variability and Misclassification from the BEES-C instrument, which addresses the number of samples (spot vs. many). OPP concludes that exposure assessment methods should be able to provide exposure estimates that are reliable and valid. However, the Framework does not incorporate a recommendation to this effect.

10. Confounding factors

This is appropriately defined and discussed. The Framework mentions that "it is not sufficient to simply raise the possibility of confounding; one should make a persuasive argument explaining why a risk factor is likely to be a confounder, what its impact might be, and how important that impact might be to the interpretation of findings."

Interpretation: This conclusion appears to be a warning to industry and other critics.

11. Statistical analysis

This is appropriately defined and discussed.

Interpretation: This is an area in which investigators may not disclose all analyses in the publication(s) or may not conduct the analyses in question. There is no discussion or guidance how to improve the status quo.

12. Potential bias in observational research

OPP recognizes that no study is devoid of bias. Most authors (and journals request) some discussion of study biases and limitations. Quantitation of the amount and direction of bias is less common. Computational tools are increasingly available to evaluate potential biases.

Interpretation: As above, there is no discussion or guidance how to improve the status quo. These are issues related to access to raw data and open discussions with investigators.

13. Interpretation of null studies

OPP states that lack of associations will be evaluated carefully. The bulk of this section states the opposite. In fact, OPP states, "the absence of evidence should not be interpreted as the evidence of absence" (page 35). The Framework mentions the effects of publication bias where the published literature disproportionately excludes null findings.

Interpretation. This section fails to account for what is already known about the risk profile of a registered pesticide. Contrary to OPP's view, the lack of human evidence, in the context of vast guideline studies, could be interpreted as evidence of absence. Furthermore, when relying upon

[6] J. Lakind et al. (2014). Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C).

published epidemiology data, OPP must account for the lack of disclosure of negative data. There is no discussion or guidance how to improve the status quo.

14. External validity (generalizability)

OPP mentions that results from one human study must be evaluated relative to another population.

Interpretation. This section is weak. OPP makes no attempt to discuss biology or human physiology. Nor does OPP apply knowledge of chemical properties of pesticides to infer exposure in different population.

V. Human incident surveillance data

OPP lists the resources for national poison control.

Interpretation. On page 38, OPP makes an important point that medical reports should be reliable, reasonable and consistent with current knowledge. However, for the incident/poison control data, OPP does not discuss the merits of using incident data that has not been classified as "definite" (i.e. eliminating probable and possible data). It is well known that many incident reports do not confirm exposure to a specific pesticide. On page 43 of the Framework, OPP states that incident data can provide useful, complementary information in evaluating the real-world risks of pesticides. The complementary nature of incident data is the key aspect. Incident data should only be considered in the context of other known data.